



Evolution of *Mycobacterium tuberculosis* complex (MTBC)

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Outline

Introduction

About MTBC & pathogenesis

Challenges in global TB control

Archaeological evidence

Evolutionary hypotheses

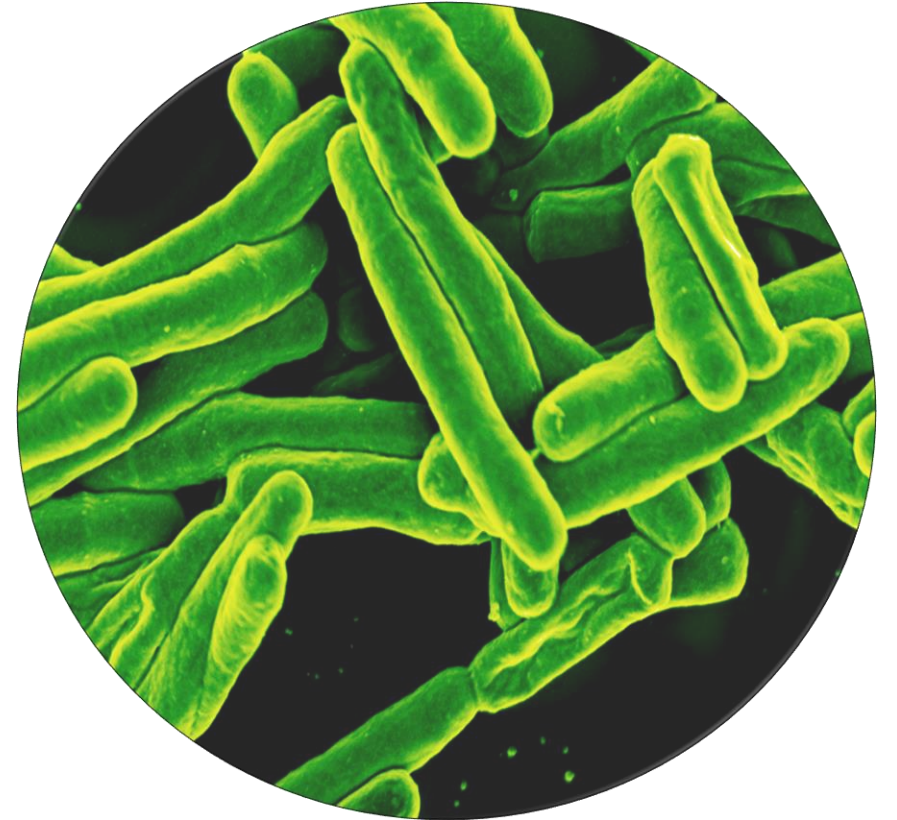
The host–pathogen interaction

HIV on the evolution of the MTBC

Human genetic susceptibility to tuberculosis

Conclusion

References



Mycobacterium tuberculosis causes widespread human tuberculosis

TB emerged ~70,000 years ago, was sporadic until 18th century epidemic

Became widespread in Industrial Revolution due to crowding/poor conditions

Incidence declined in 20th century in developed nations with better conditions

Incidence increased again in 1980s due to HIV, urban health issues, antibiotic resistance

Introduction

Introduction



More than 10 million people continue to fall ill with TB every year



5.8M men, 3.5M women, 1.3M children



TB present in all countries/ages



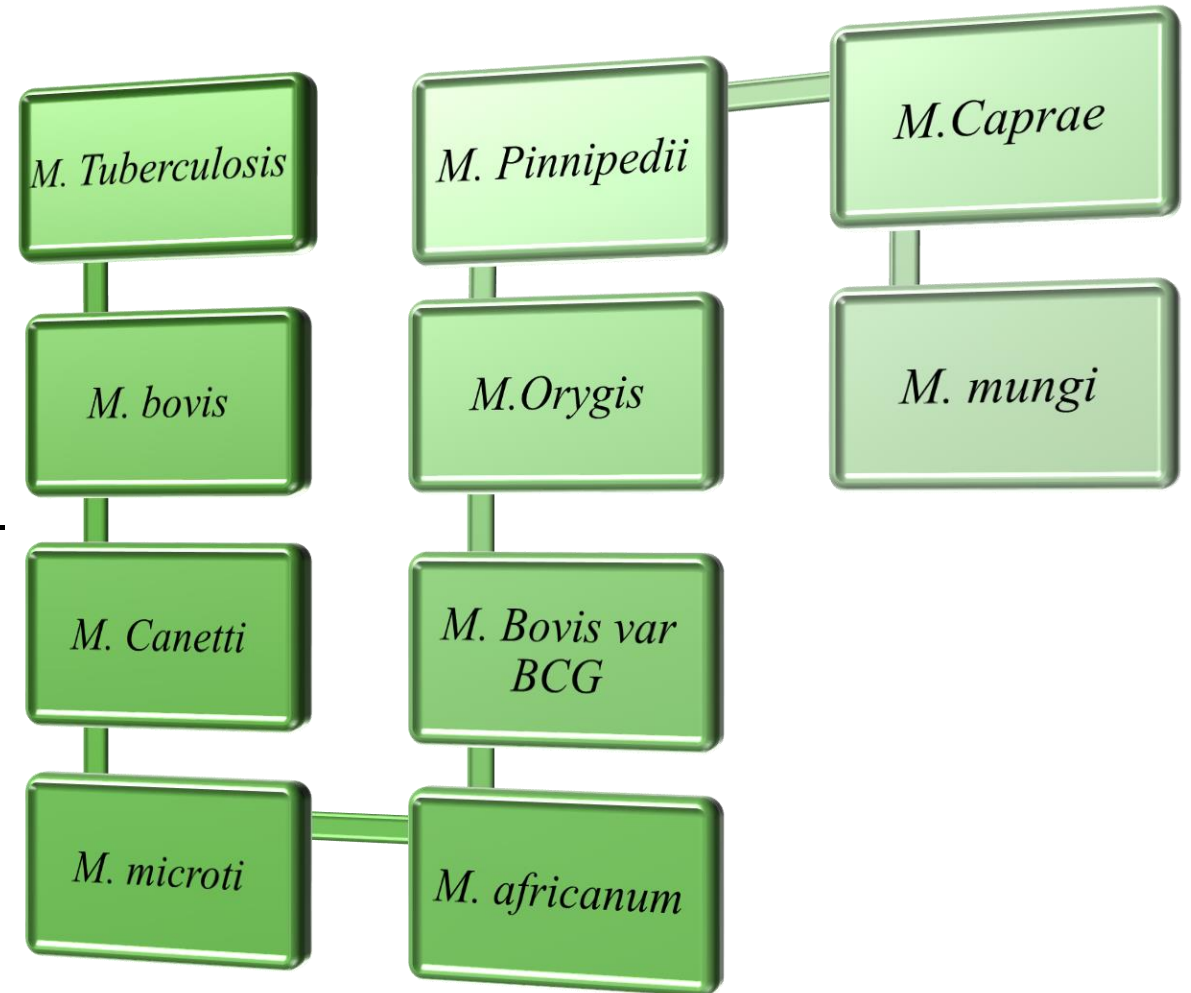
TB is 2nd leading infectious killer globally after COVID-19



The human pathogen evolved complex immune evasion strategies from environmental ancestors

MTBC

- ✔ Genetically closely related group of bacteria causing tuberculosis across a wide range of hosts
- ✔ Rod-shaped, acid-fast, aerobic, and slow-growing intracellular pathogens
- ✔ Subvert and escape the host immune system by disrupting phagosomal cells



MTBC

Table 1

Overview of the members of *Mycobacterium tuberculosis* complex (MTBC) with their basic characteristics (Forrellad et al., 2013; Pfyffer, 2015).

MTBC species	General Descriptions
<i>M. tuberculosis</i>	<ul style="list-style-type: none">- Most familiar species.- Infecting greater than 1/3 of the world's human population.- Able to infect animals that are in contact with humans.
<i>M. canettii</i> and <i>M. africanum</i>	<ul style="list-style-type: none">- Close relation with <i>M. tuberculosis</i>.- Can also cause human tuberculosis.- Generally isolated from African patients.
<i>M. bovis</i>	<ul style="list-style-type: none">- Displays the widest spectrum of host infection.- Affecting domestic or wild goats, bovines and humans.
<i>M. bovis</i> var <i>BCG</i>	<ul style="list-style-type: none">- A laboratory-selected mutant form of <i>M. bovis</i>.- Sole vaccine used for TB prevention during early childhood.
<i>M. caprae</i>	<ul style="list-style-type: none">- Isolated only from goats.
<i>M. microti</i>	<ul style="list-style-type: none">- Pathogen from rodents.- Isolated from voles usually (rodents from genus <i>Microtus</i> or related genera).- Can lead to disease especially in immunocompromised human patients.
<i>M. pinnipedii</i>	<ul style="list-style-type: none">- Infects seals.
* <i>M. mungi</i>	<ul style="list-style-type: none">- The causative agent of tuberculosis in banded mongoose (<i>Mungo Mungo</i>).
* <i>M. orygis</i>	<ul style="list-style-type: none">- Affects bigger mammals, such as waterbucks, antelopes, oryxes and gazelles on the African continent.

MTBC

Mycobacterium tuberculosis complex has several nearly identical species

Identical 16S rRNA sequences proves common ancestor

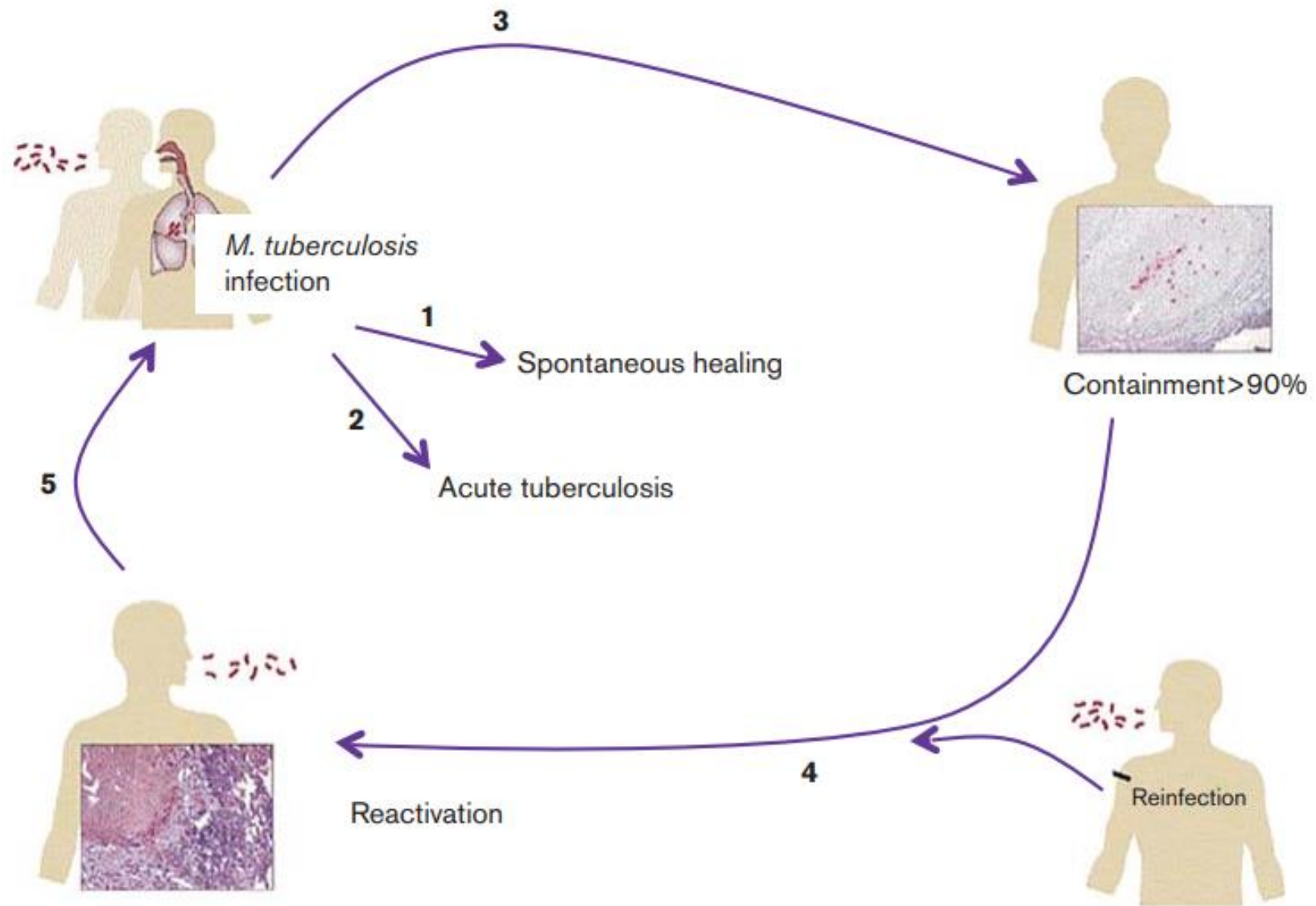
Differ in epidemiology, host range, virulence, immune evasion strategies

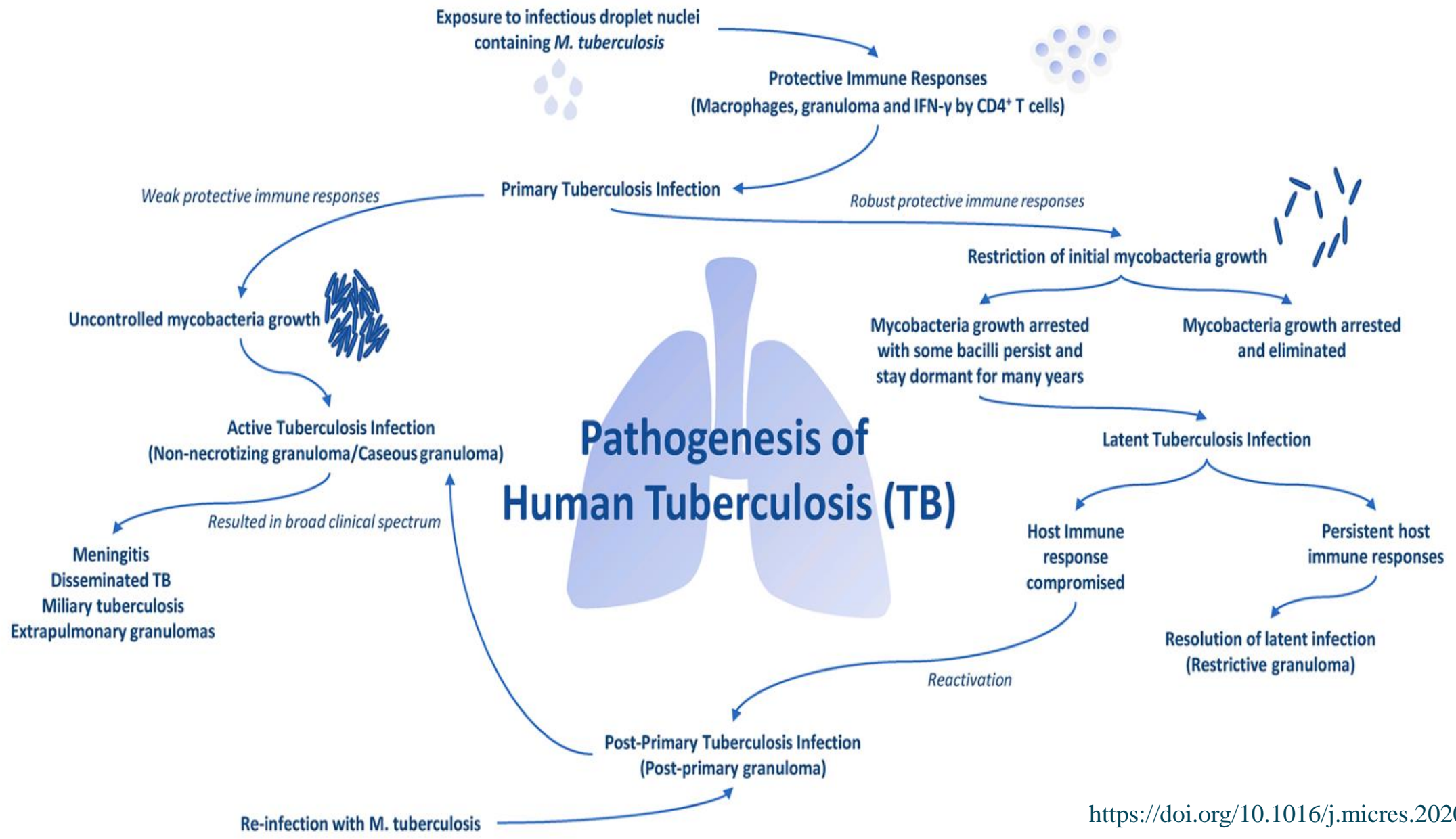
MTB complex's success stems from ability to persist latently

Latent infections act as reservoirs to spread/reactivate opportunistically

A microscopic view of numerous blue, rod-shaped bacteria, likely Bacillus anthracis spores, scattered across the frame. The bacteria are in various orientations and some are in sharp focus while others are blurred in the background.

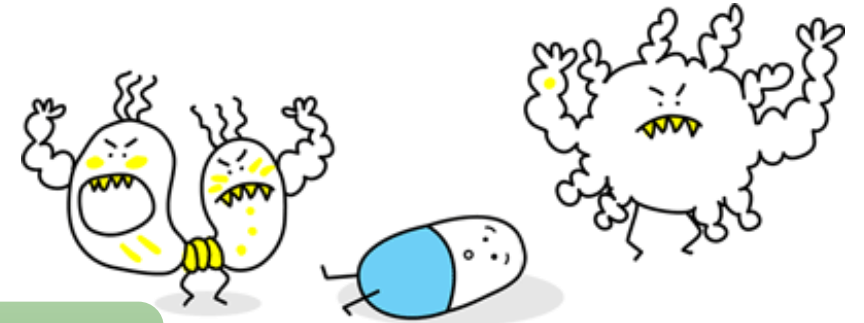
About pathogenesis



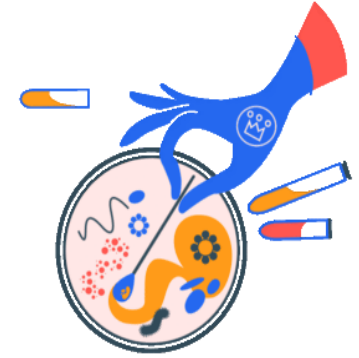


Obstacles and challenges in global TB control

- Social/Health Challenges
 - HIV/AIDS coinfection (1.2M patients)
 - Population movement
 - Multidrug-resistant (MDR) strains (500K cases)
 - Extensively drug-resistant (XDR) strains (27K cases)
 - Totally drug-resistant strains emerging



Obstacles and challenges in global TB control



Identifying
and treating
all cases

120-year-old
microscopy
diagnostic

100-year-old
vaccine
(BCG)

40-60 year old
drugs

Obstacles and challenges in global TB control



Minimal genotypic/phenotypic variation



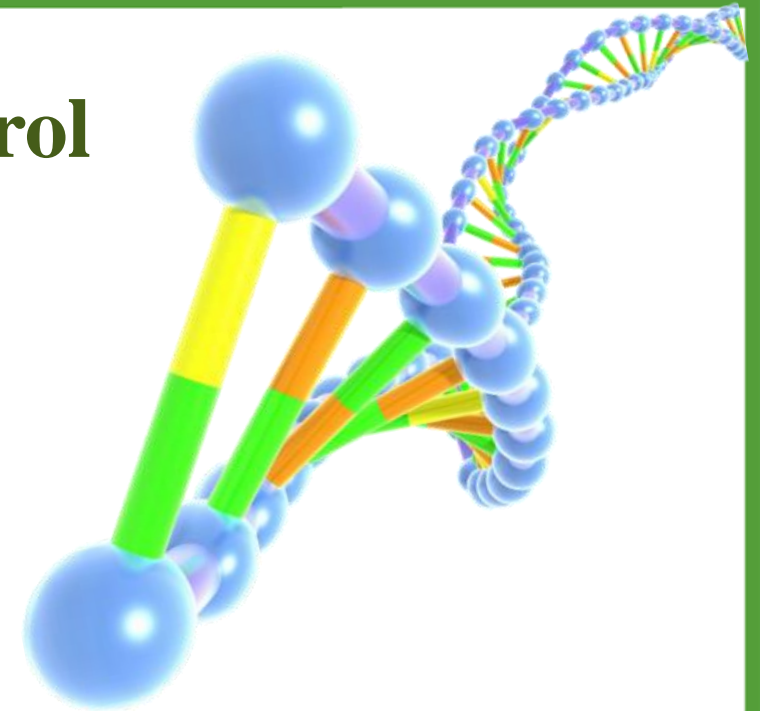
Highly clonal, 99% sequence identity



Investigated by MLST, NGS, WGS methods



WGS used to study genetic diversity



MLST: Multilocus sequence typing

NGS: Next-generation sequencing

WGS: Whole-genome sequencing



**Human-adapted
MTBC is unique**

**Without any
environmental or
animal reservoir**

**Cause disease to
transmit between
individuals**

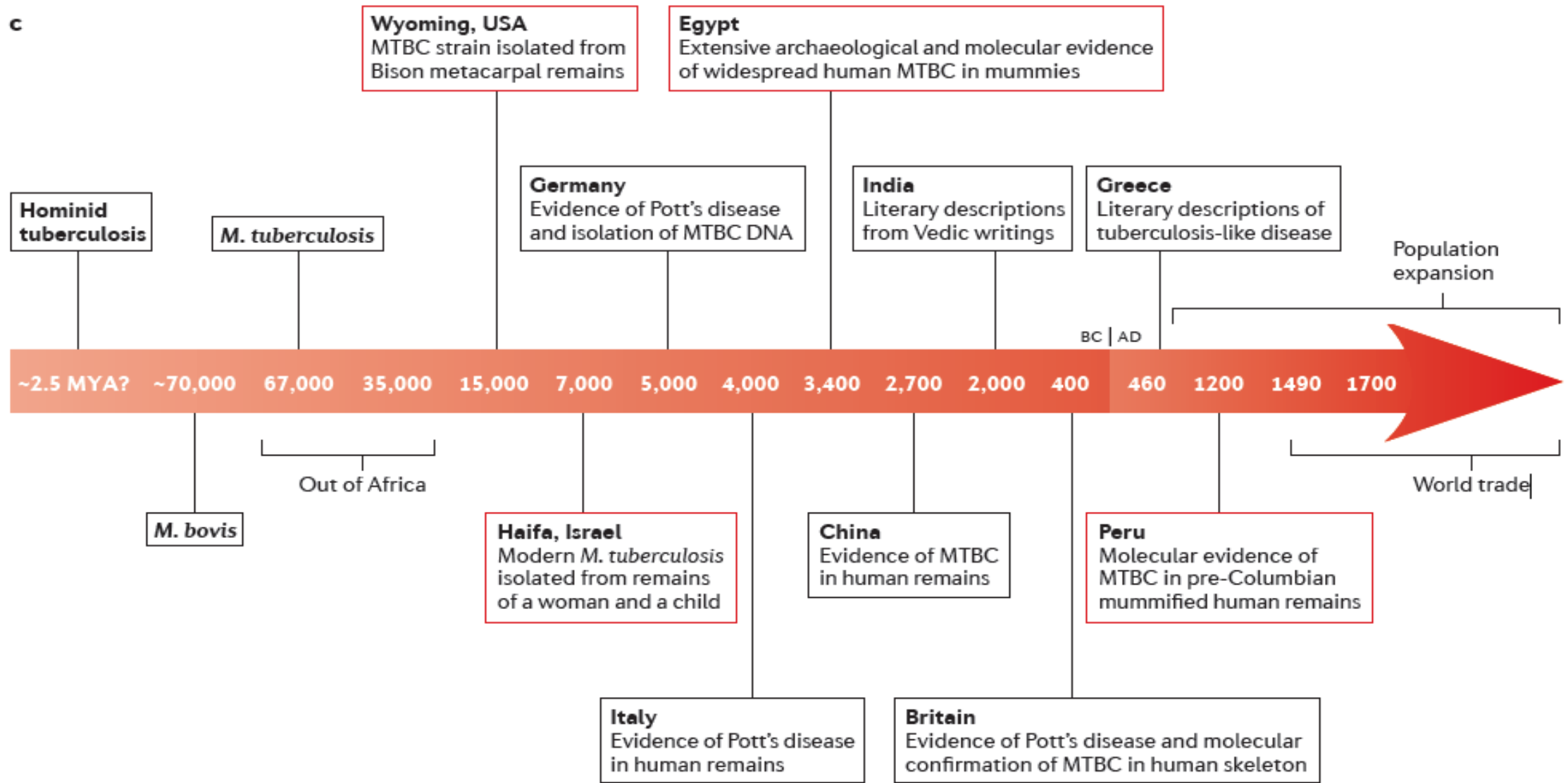


How did the MTBC evolve to become such a successful pathogen?



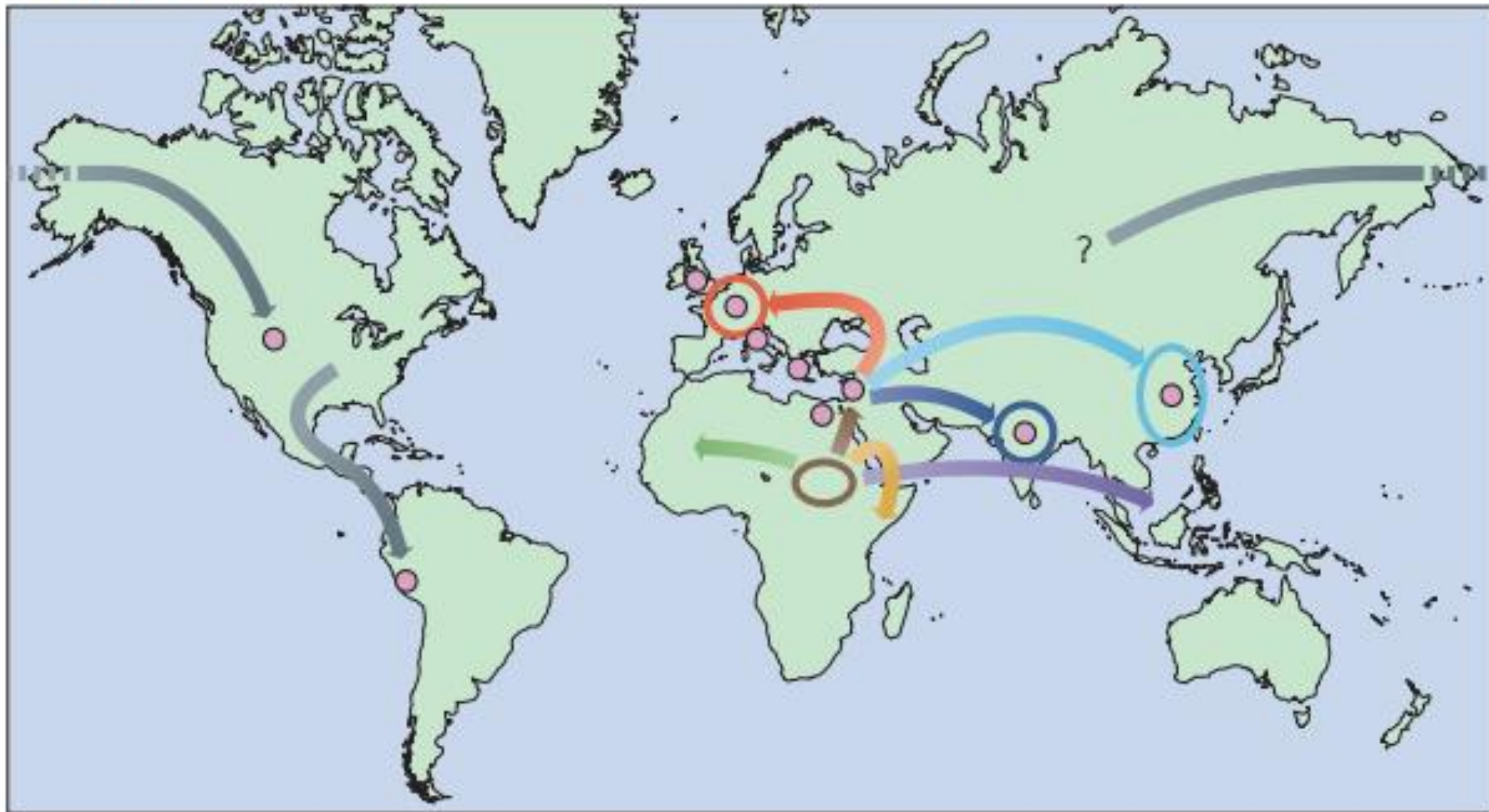
**Hypothesized evolutionary scenario for *Mycobacterium tuberculosis*
and archaeological evidence**

c



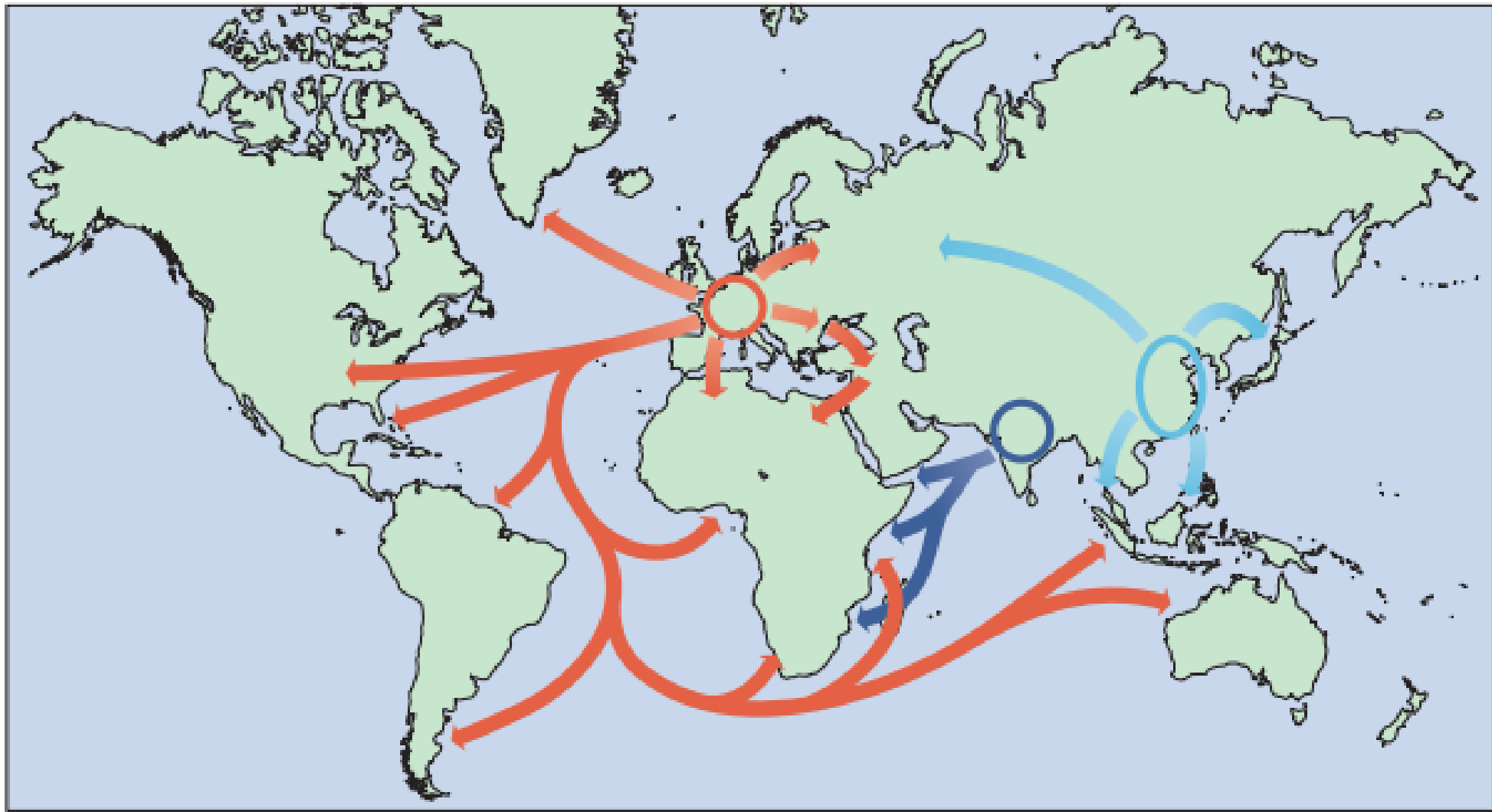
doi:10.1038/nrg3664

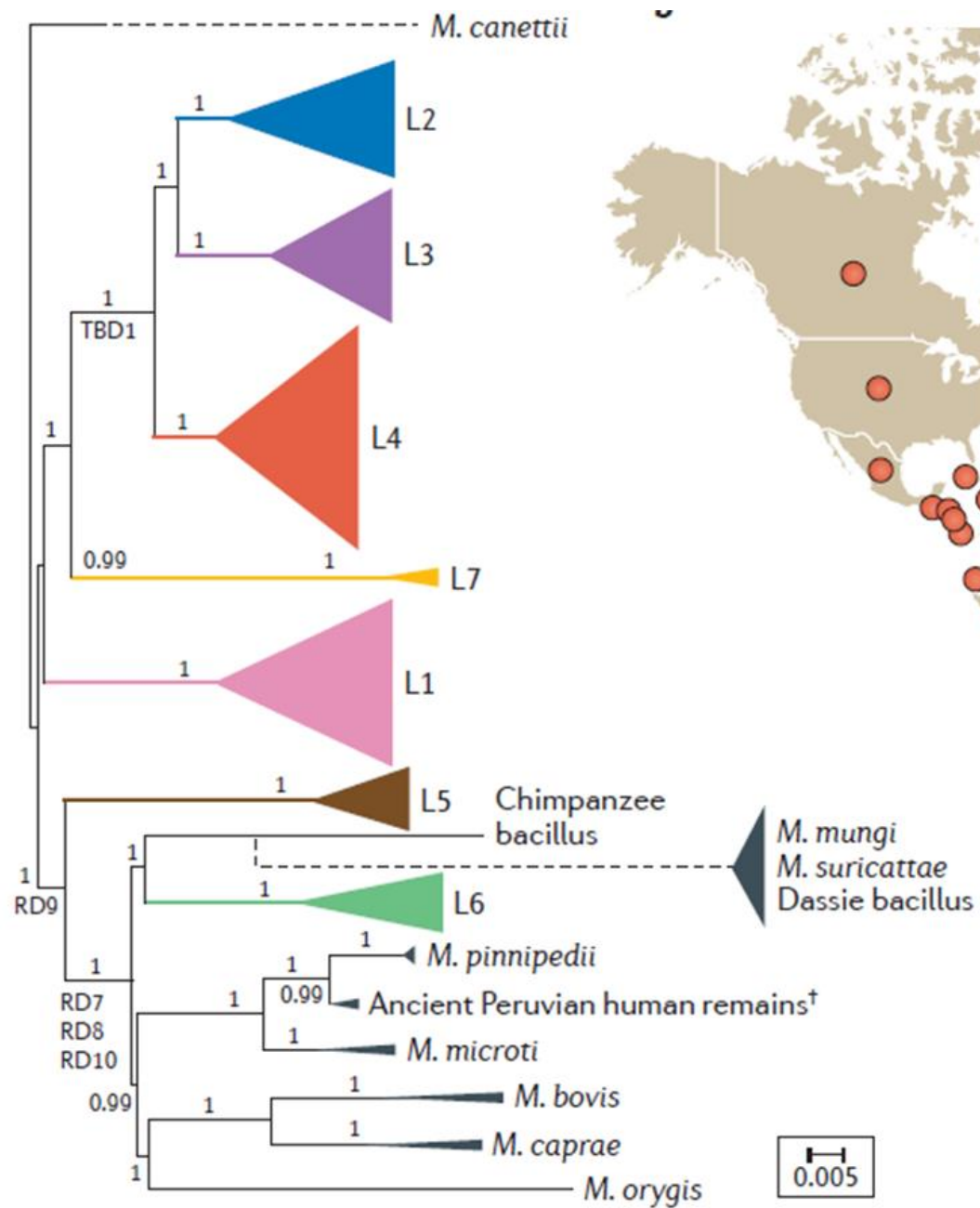
a Before AD 1200



doi:10.1038/nrg3664

b After AD 1200





doi:10.1038/nrmicro.2018.8

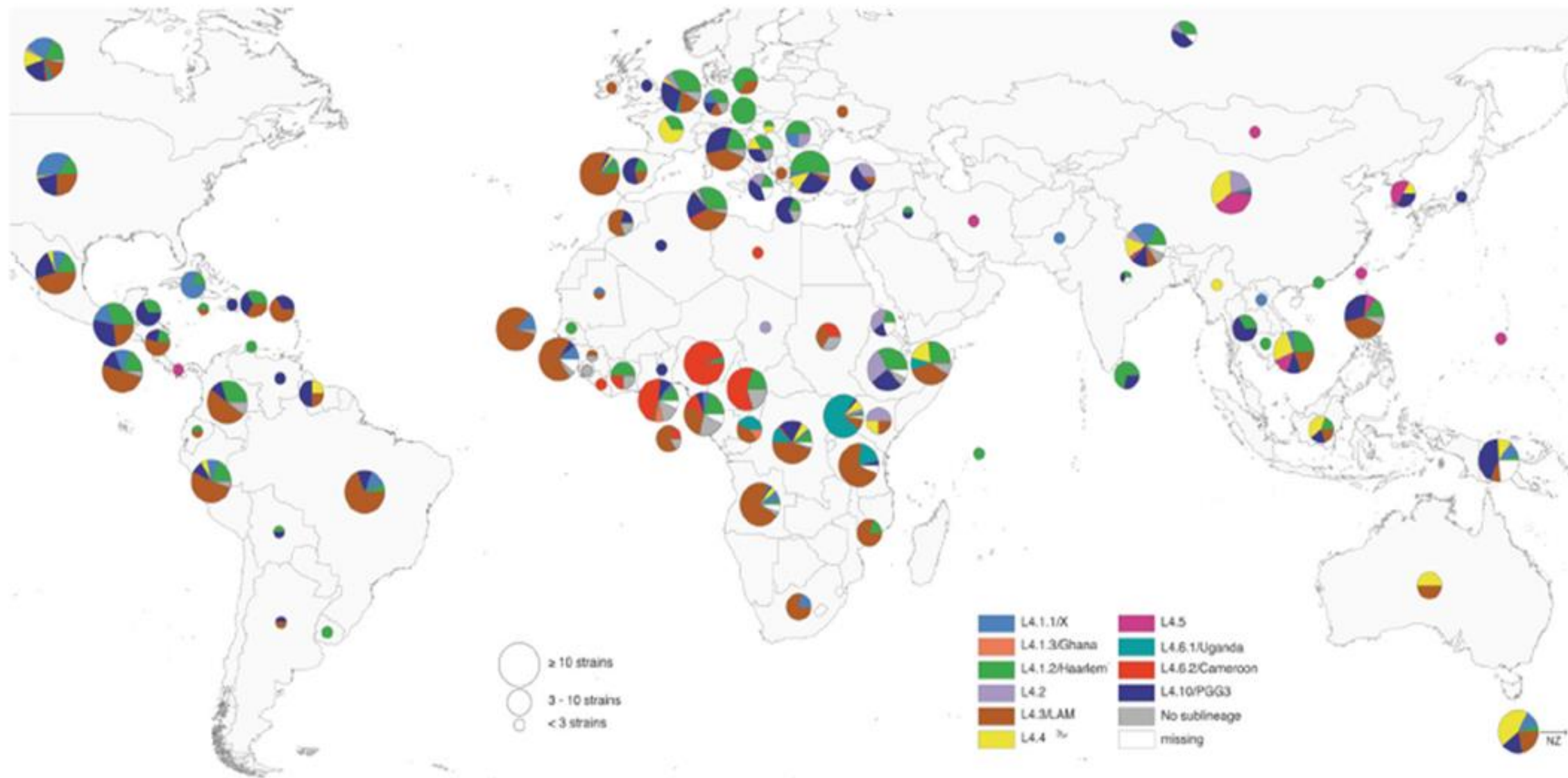
The ecology of the human-adapted MTBC

Generalists

Occupying many
different
ecological niches

Specialists

Narrow niche
that corresponds
to their specific
host population

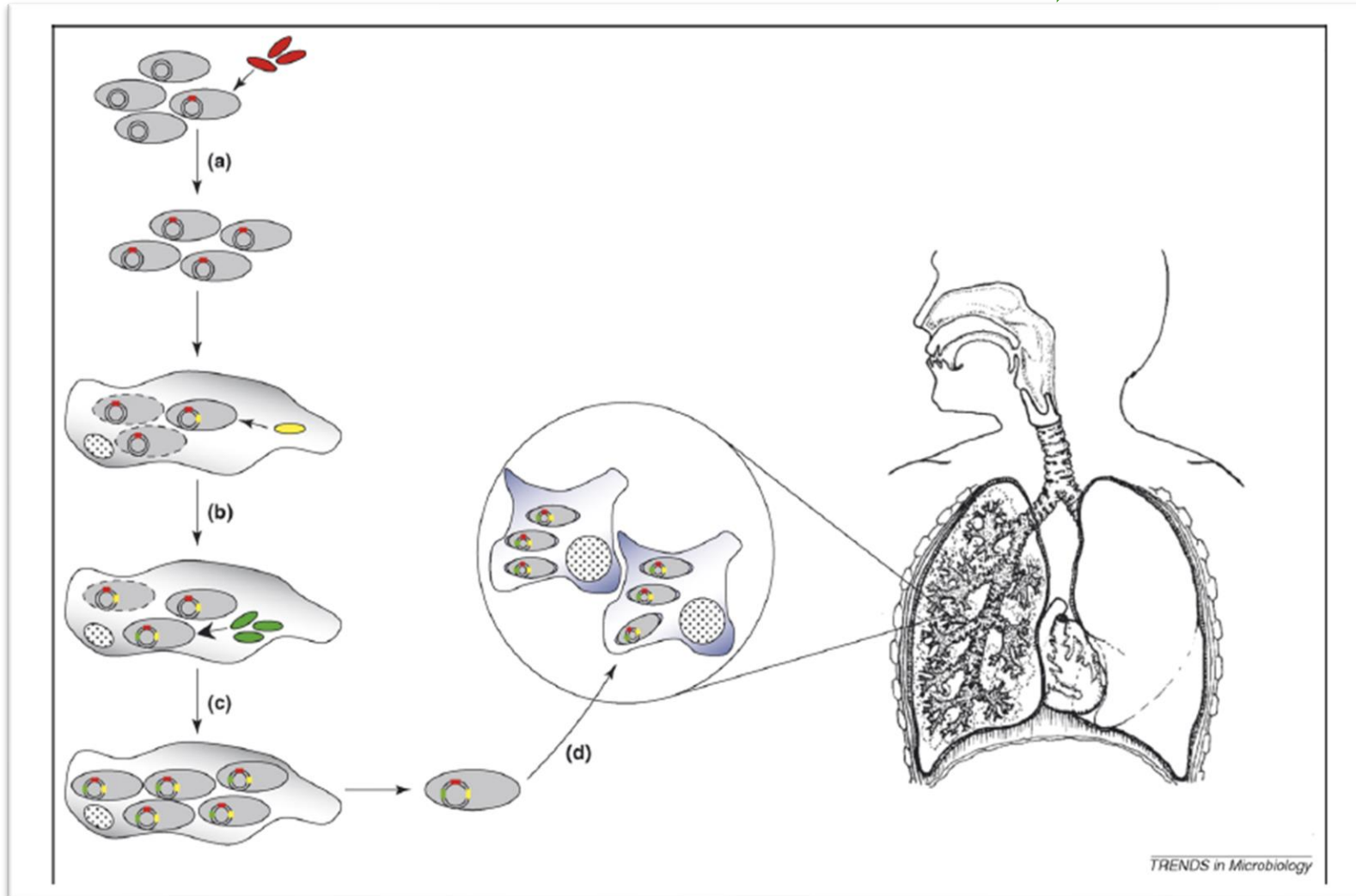
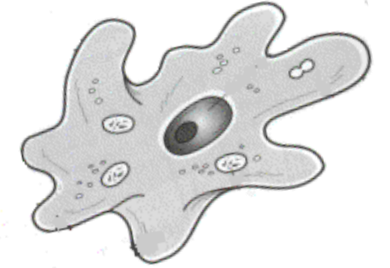


doi:10.1038/nrmicro.2018.8

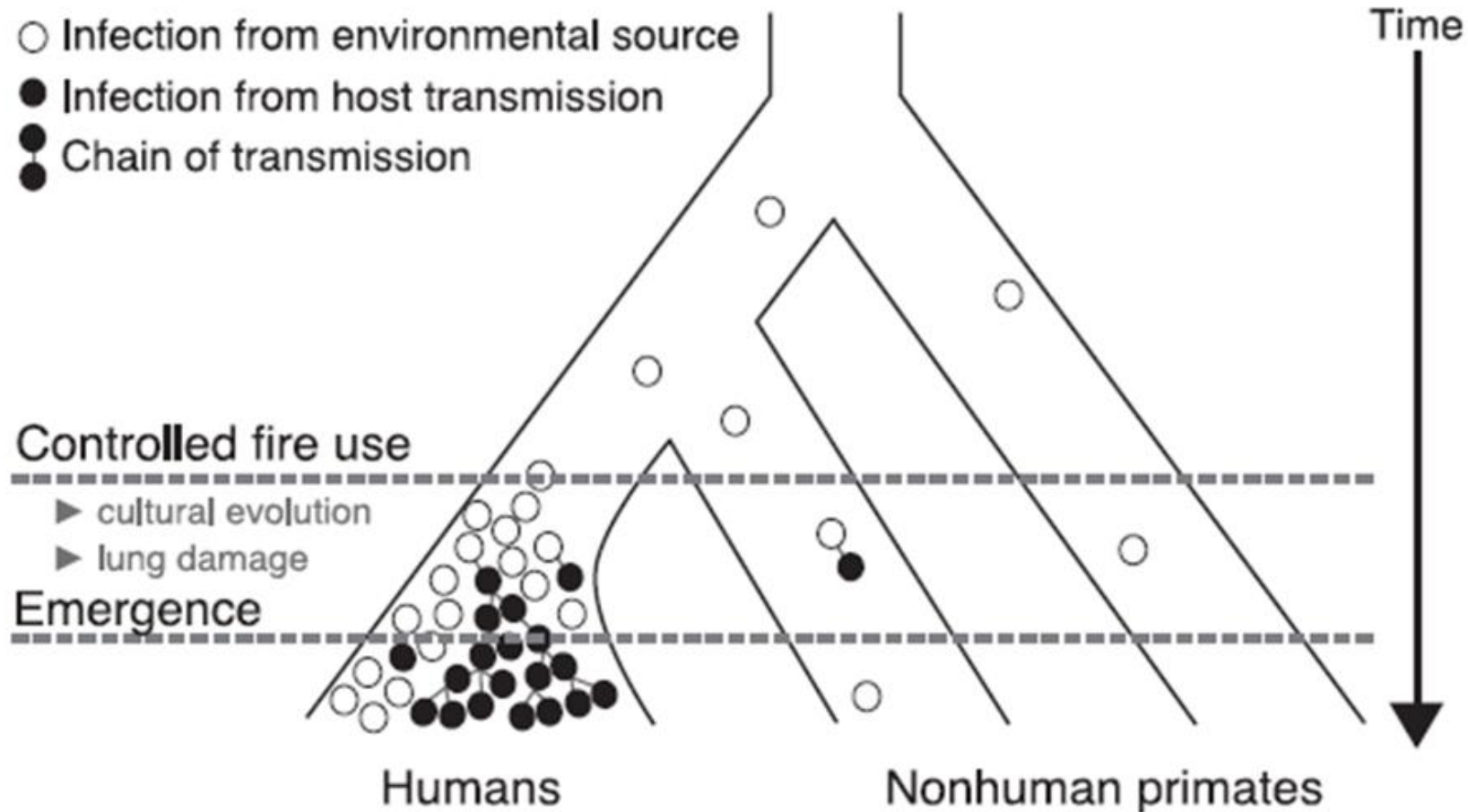
A microscopic view of numerous blue, rod-shaped bacteria, likely Bacillus anthracis spores, scattered across the frame. The bacteria are in various orientations and some are in sharp focus while others are blurred in the background.

From an environmental organism to a professional pathogen

Did protozoa 'teach' mycobacteria to become virulent?



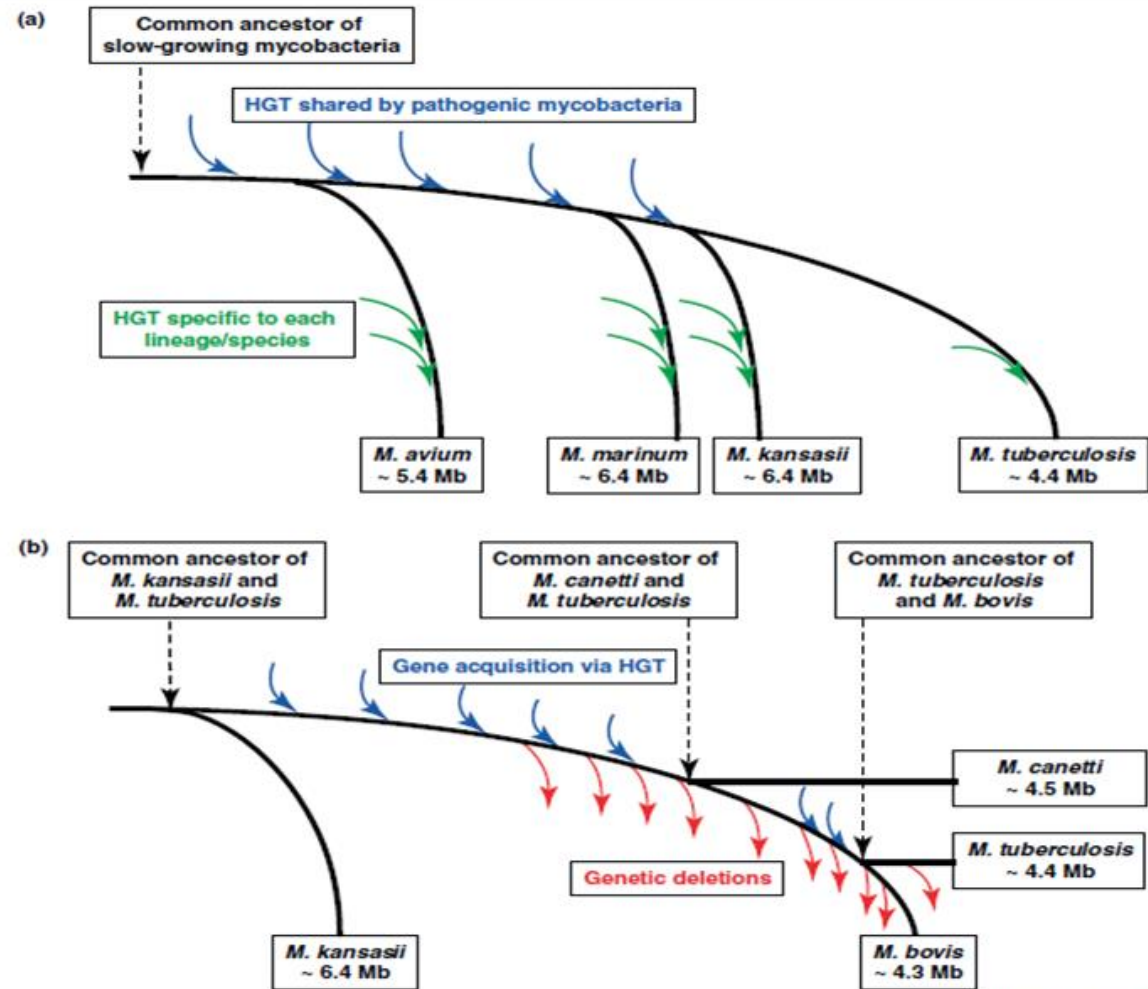
➤ **Controlled fire use by early humans may have contributed to the evolution of TB transmission**



<https://dx.doi.org/10.1073%2Fpnas.1603224113>

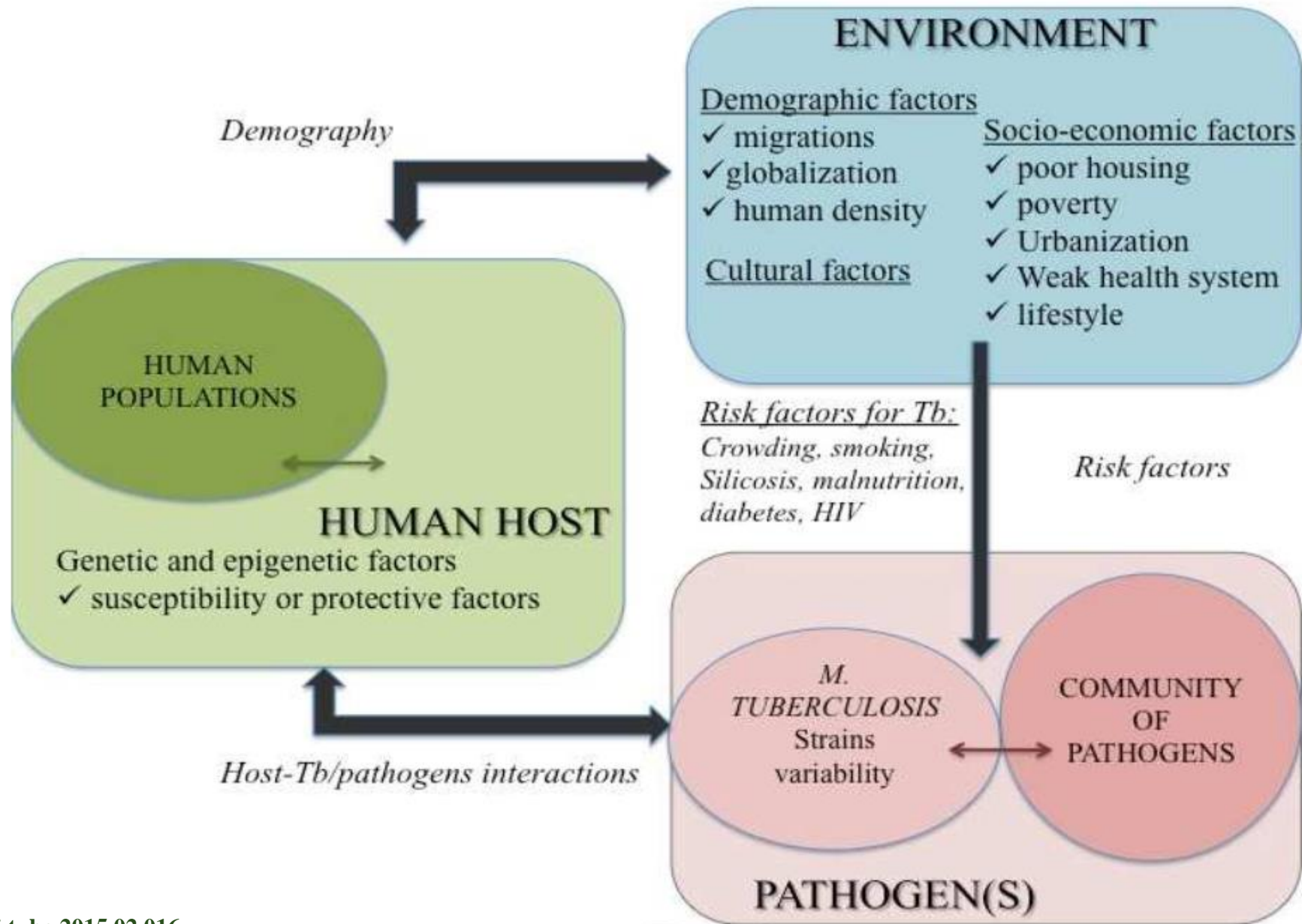
✓ What were the genetic changes that enabled the transition of the MTB ancestor to a professional pathogen?

- Genome downsizing through deletion of genes.
- Acquisition of new genes through horizontal gene transfer (HGT).

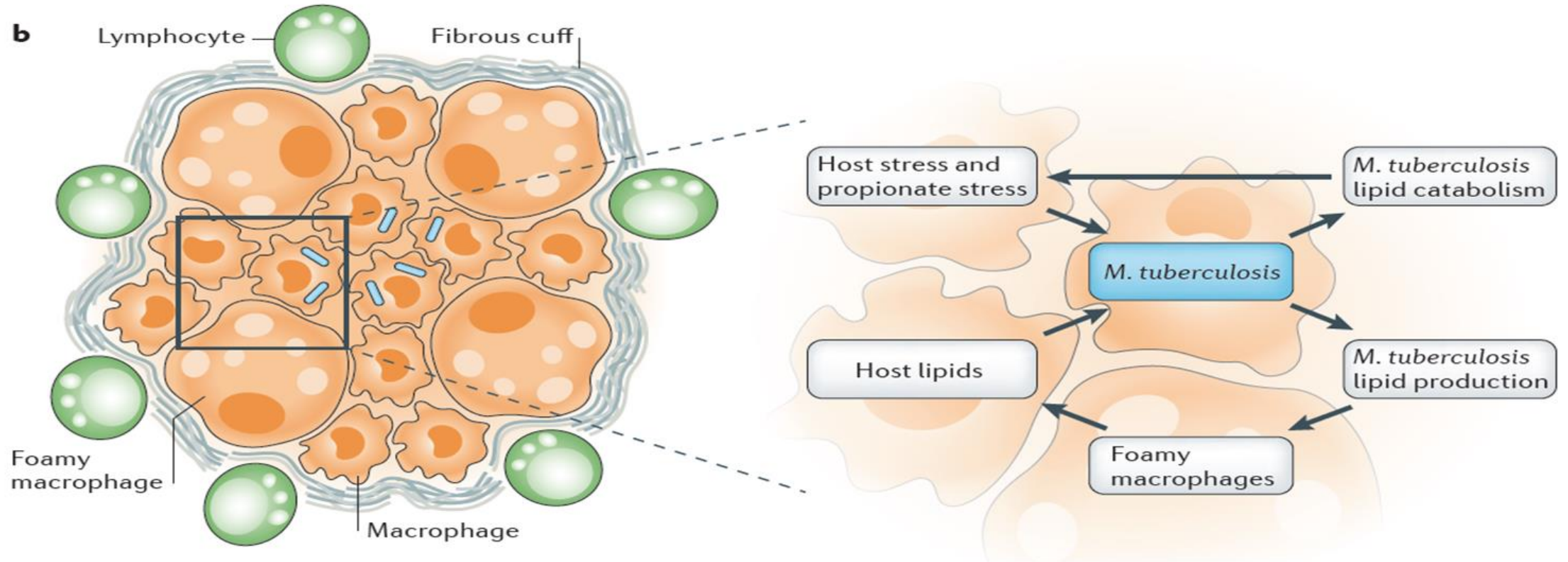




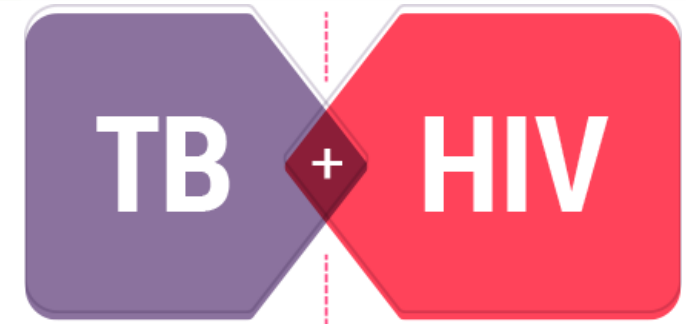
Wide range of factors influences TB epidemics



The host-pathogen interaction



Impact of HIV on the evolution of the MTBC



Increased transmission and spread

- HIV weakens the immune system, leading to more TB cases worldwide
- Provides more opportunities for genetic variation and evolution

Selective pressure for drug resistance

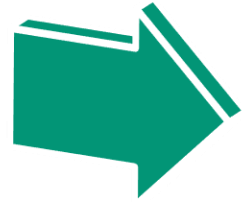
- Challenging treatment of HIV-associated TB due to drug interactions and prolonged regimens
- Emergence and spread of drug-resistant MTBC strains

Impact of HIV on the evolution of the MTBC



Adaptation to immunocompromised hosts

- MTBC strains may evolve to adapt to the weakened immune environment
- Potential evolution of increased virulence, immune evasion strategies, or improved persistence



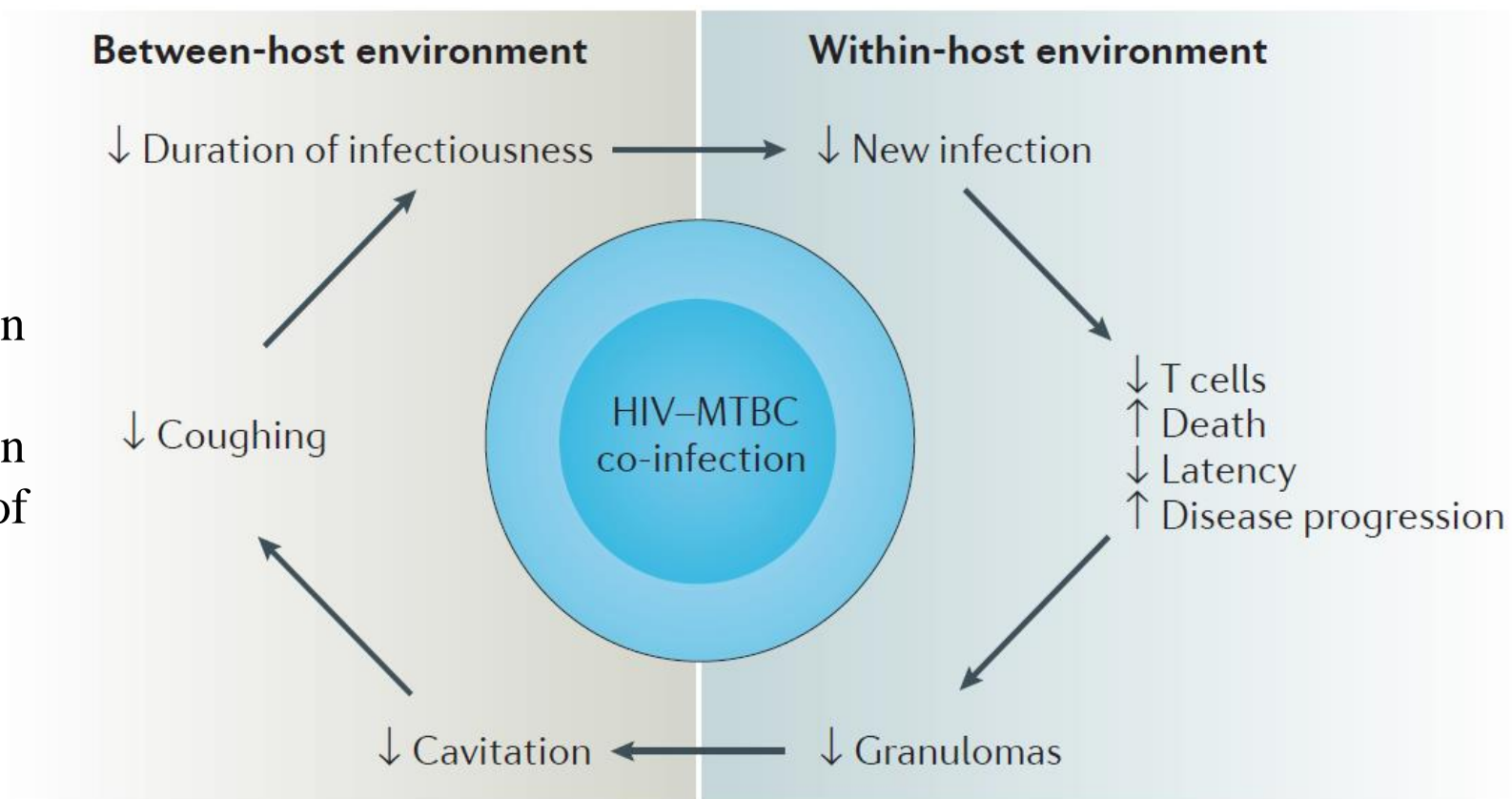
Increased genetic diversity

- High TB transmission rates in HIV-infected populations
- Selective pressures from drug treatment and host immune status
- Larger pool of genetic variants for natural selection

Impact of HIV on the evolution of the MTBC

Three studies have been published on the subject

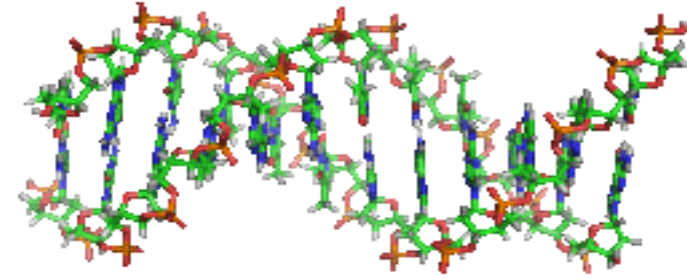
1. HIV co-infection had no effect on the mutation rate.
2. HIV co-infection had no effect on the overall population structure of the MTB.
3. More mutations with T cells, implies T cell immunity drives MTBC diversity.





Human genetic susceptibility to tuberculosis

Host Genetic Factors in TB



Host genetics, bacterial strains, environment influence TB risk/drug response

Only ~10% of infected develop active disease, most remain latent

Studies link polymorphisms in immune genes to increased TB susceptibility:

CCL2, NRAMP1, IRGM1, IL-8, TLRs, NOD2

These alter immunity, conferring genetic predisposition to TB

NRAMP1 Gene and TB Susceptibility

Expressed in macrophages, lymphocytes, lungs

Encodes divalent metal ion transporter protein

Fe⁺⁺ transported by NRAMP1 inhibits MTB growth

Nonfunctional NRAMP1 mutations impair intracellular killing of MTB by macrophages

Contributes to increased host susceptibility to TB disease

MicroRNAs dysregulation In tuberculosis Infection



Gene expression profiles differ in macrophages, NK cells from active TB, latent TB, and healthy controls



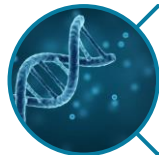
miRNAs regulate T cell differentiation/function



miRNAs also regulate innate functions of macrophages, dendritic cells, NK cells



Innate immune response against TB regulated by miRNAs



Differential miRNA expression reflects TB disease progression/activity



Host miRNA expression patterns altered by MTB infection

Conclusion



TB remains a major global health issue

Deeper understanding of pathogenesis, host-pathogen interactions, and drug resistance evolution is crucial

Tracing gene gains and losses elucidates the intricate evolutionary paths of MTB

Exploring evolutionary hypotheses can aid better prevention and treatment

Conclusion



HIV/AIDS epidemic increases TB risk,
requires further study



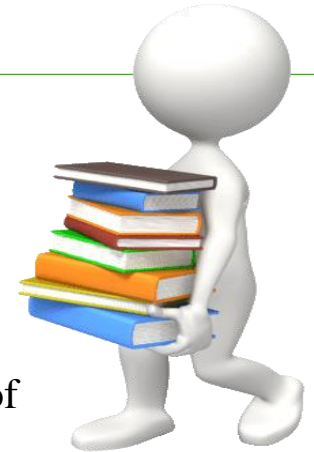
Consider host factors: genetic
susceptibility, microRNA effects on
immunity



Multidisciplinary efforts combining
molecular studies, epidemiology,
immunology, etc. are needed for better
understanding and control strategies

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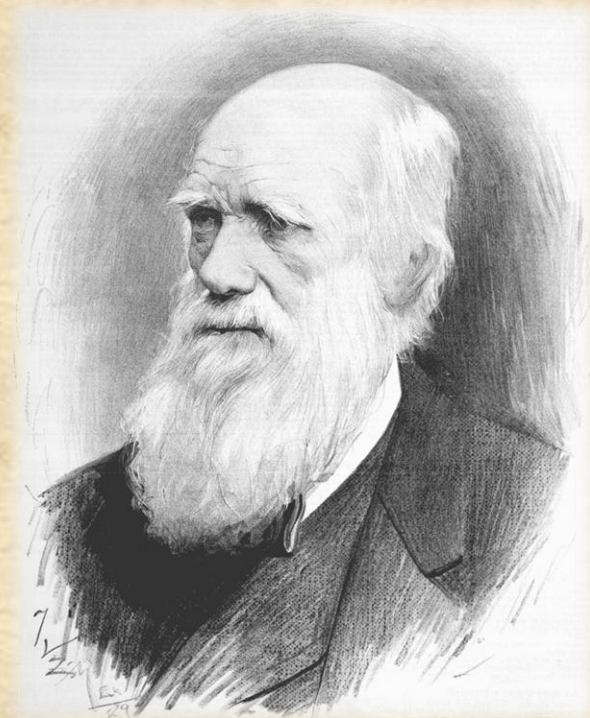
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- “It is not the most intellectual of the species that survives, it is not the strongest that survives, but the species that survives is the one that is able to adapt and adjust to the changing environment in which it finds itself.”

Charles Darwin



Thank you for your attention 😊

